High intensity sweeteners chemicals structure, properties and applications
Osama Ibrahim1*

Abstract
High Intense sweeteners (HIS) are commonly used as a sugar substitutes or sugar alternatives and provide sweet without calories. HIS are in high demands due to its multiple advantages including assisting people in losing weight or avoiding obesity and assisting diabetics to control their blood sugar level. The first known intense sweetener is Saccharine that was discovered in the year 1878. Since then scientists discovered several other intensive sweeteners that are sweeter than sucrose with zero calorie. Some discovered sweeteners are Plants extract (Steviol glycosides, and Mogrosides), semi-synthetic peptides (Aspartame, Neotame, and sucralose), and synthetic chemicals. (Saccharine, Acesulfame-K, and Cyclamate).

These High intensive sweeteners have been approved as safe for applications (1) in foods, beverages, dietary supplements, and pharmaceuticals products by Food and Drug administration (FDA) (2) in United States and by other similar agencies in other countries (3). The levels of these non-nutritive high intensive sweeteners used in foods, beverages, dietary supplements, and pharmaceutical products are based on the approved daily intake (ADI) by FDA and by other safety authorities worldwide. This ADI level is 100 fold lower than the safe dose demonstrated in laboratory studies. It is estimated that the global demand of HIS is exceeding 9.0 billion dollars and growing. The only HIS that is declining in global market is the old discovered sweetener Saccharine.

Keywords: High intensive sweeteners, natural sweeteners, artificial sweeteners, Saccharine, Aspartame, Acesulfame-K, Cyclamate, Sucralose, Neotame, Steviol glycosides (Rebaudioside-A), and Tri-terpine glycoside (Mogroside-V)

Introduction
High Intensive sweeteners (HIS) are commonly used in food products, beverages and some oral pharmaceuticals as sugar substitutes or sugar alternatives (4) All high intensive sweeteners (HIS) are zero calories and hundreds time sweeter than sucrose.

HIS produced from natural sources are recognized by FDA as safe with GRAS status (Generally Recognized As Safe) (4). These HIS with GRAS status does not require FDA approval and can be used in foods and other applications after submitting a GRAS notice to FDA. The GRAS statutes of these HIS are determined as safe because they are naturally occurred in plants or produced from non-pathogenic microorganism. This safety standard of GRAS status are defined in FDA’s regulations and scientists must determine that a sweetener with GRAS status meet the safety standard of reasonable certainty no harm to consumers under the intend conditions of its use.

GRAS notices have been submitted to FDA for two types of high-intensity sweeteners. These two types are certain steviol glycosides extracted from the leaves of the stevia plant Stevia rebaudiana and morgosides extracted from Luo Han Guo (Monck fruit) Siraitia grosvenori Awingle.

HIS produced from non-natural sources by semi-synthetic or synthetic chemistry process must undergo premarket review and approved by FDA before it can be used as food additives in foods or other applications. The Six high-intensity sweeteners that required such approval by FDA in the United States as food additives are Saccharine, Aspartame, Acesulfame K, Sucralose, and Cyclamate.

High intensive sweeteners with GRAS status
These are the two natural High intensive sweeteners of Steviol glycosides and Mogroside that did not require FDA approval because both are extracted from plants and determined as safe. The following are chemicals structure and properties of these two natural high intensive sweeteners (HIS) of Steviol glucosides and Mogrosides.
1. Steviol glycosides:

Steviol glycosides (5) are natural extract of the leaves of Stevia rebaudiana a native plant to part of South America and commonly known by the name Stevia (6). Steviol glycosides (7) are non-nutritive zero calorie sweeteners accompanied by after taste and are reported to be 200 to 400 sweeter than sucrose depend on the type of application and formulation.

There are two chemical structures of Steviol glycosides extract from Stevia leaves known by the name Stevioside and Rebaudioside-A. Both Stevioside and Rebaudioside-A are the two extracts with intensive sweeteners in the stevia leaf.

2. Mogrosides

Mogrosides are extracted from the plant LUO HAN GUO which also known by the name Monk fruit (9). Both names are the common names for the plant Sarmatia grosvenorii that is grown predominantly in the southern mountains of Guangxi province, southern China.

Monk Fruit has been cultivated and consumed in China for hundreds of years with no harm to the consumers. It is sold in China as a sweeteners and flavour ingredient for foods and beverages, as well as used in traditional Chinese medicine for hundreds of years.

In the year 2008, the FDA recognized only Rebaudioside-A, as safe with GRAS status (8) for foods, beverages and other applications. Its acceptable daily intake (ADI) is 4 mg/kg body weight.

The chemical structure of Rebaudioside-A which is also known by the name Reb-A or Rebiana-A has one beta-D-glucose replacing the bottom hydrogen atom of steviol glycoside and a chain of three beta-D-glucose molecules replacing the top hydrogen site of steviol glycoside.

This sweetener Rebaudioside-A (RebA or Rebiana A) is blended with the sugar alcohol erythritol and marketed in United States under trade name Truvia®.

The fruit is a truly natural, and its extract contains a mixture of five chemical structures known by the name mogrosides. There are five chemicals structure of mogrosides (I, II, III, IV, and V), these numbers are the number of glucose units that are attached to the chemical structure of mogroside unit. All mogrosides are zero calorie sweeteners and 100 to 250 times sweeter than sucrose. The level of mogrosides sweetness depends on the percentage of mogroside-V (9) in the total mixture of mogrosides. Mogrosides mixture are Generally Recognized As Safe (GRAS) by FDA and is available in the market in the form of
liquid or solid form under the trade name Purefruit® as sweetener and flavour enhancer for food products, beverages, chewing gums, backed goods, dietary supplements, powdered drinks, national bars, and chocolates.

High intensive sweeteners approved by FDA:
High intensive sweeteners that are produced from non-natural sources must undergo premarket review for approval by FDA before it can be used as food additives in foods or other applications. These are the two semi-synthetic peptides of Aspartame and Neotame, and the four synthetic Chemicals of Saccharine, Sucralose, Acesulflame Potassium and Cyclamate.

The following are the chemicals structure and properties of these Six HIS that are approved by FDA in the United States as food additives.

A. SEMI-SYNTHETIC PEPTIDES:
Both Aspartame and Neotame are manufactured by two production steps. The first step is the microbial fermentation process for separately producing the two amino acids aspartic acid and phenylalanine, the second step is the synthetic chemical process for forming the peptide bond between these two amino acids and side chains.

The non-pathogenic microorganism for the production of aspartic acid by fermentation is the bacteria B. flavours and the non-pathogenic microorganism for the production of phenylalanine by fermentation is the bacteria C. glutanicum .

In the synthetic chemical process only L- form for both amino acids are selected for forming peptide bond between the carboxylic group of L-aspartic acid and the amine group of L-phenylalanine.

1. Aspartame:

Aspartame is approved in 1981 for use under certain conditions as a table top sweetener, and as sweetener for a wide variety of foods, including chewing gum, candies, cold breakfast cereals, beverages, drinks, and desserts. It is not suitable for baked goods or any other products required heating during its production process or before service. This heat instability of Aspartame is due to its dipeptide structure. The heat breakdowns the dipeptide bond into the two free amino acids L-aspartic and L- phenyl alanine. Breaking down this dipeptide bond causes the loss of Aspartame sweetness property.

Aspartame is metabolized in the human digestive system into its two amino acid of phenyl alanine and aspartic acid. People with the rare disease of disorder phenylketonuria (PKU) (12) cannot metabolize phenylalanine and should avoid aspartame in their diets. Due to this rare disease, Aspartame-containing foods and beverages must be labelled to inform individuals with PKU that the product contains phenylalanine.

Acceptable daily intake (ADI) of Aspartame is 33 mg/kg body weight and it is available in the market under brand names NutraSweet®, and equal®.

2. Neotame:

Neotame (13) is a modified form of Aspartame, created by combining it with another chemical. This makes it more stable, sweeter and prevents it breaking down into phenylalanine during the metabolic process.

It is approved by FDA for use as sweetener and flavour enhancer in food products and beverage. It is marketed under the brand name Newtame®.

Neotame is a zero calorie sweetener with about 8,000 to 13,000 times sweeter than sucrose depends on its application and formulation. It is chemically similar to aspartame, but it is more sweetener and more stable than aspartame. Neotame stability is due to the 3, 3-dimethylbutyl group attached to the amino group of the amino acid aspartic acid.
This attached 3, 3-dimethylbutyl group to aspartic acid block peptidase enzymes in the digestive system to hydrolyze the peptide bond into the two free amino acids aspartic acid and phenyl alanine. This peptidase enzyme resistance makes Neotame safer for individuals with the rare disease of disorder phenylketonuria (PKU) and help manufacturers to eliminate the warning label that the product contains phenyl alanine (13).

Neotame is metabolized in human system into methanol and di-esterified peptide residue. The amount of methanol released in human blood stream is very low due the low level of Neotame used as sweetener in foods, beverages and other applications.

3. **Sucralose:**

![Sucralose Structure](image_url)

**Tri-clo-hloro-galacto-sucrose**

Sucralose (16) is a common name for a new high intensity sweetener derived from sucrose. It is about 600 times sweeter than sucrose and produced by the selective chlorination of sucrose.

It is safe for human consumption (17) approved by FDA (18) in United States and also approved in more than 35 countries by other similar organizations. Its acceptable daily intake (ADI) (19) is 15mg/kg body weight.

Sucralose is a non-chloric, that does not breakdown in the body into the two monosaccharides glucose and fructose and does not promote tooth decay (20). It is soluble in water and has excellent stability in wide range of PH and temperature. These properties (21) make Sucralose suitable for wide applications (22) including processed food and beverages. It is available as a tabletop sweetener under the trade name Splenda®.

**B. SYNTHETIC CHEMICALS:**

1. **Saccharin:**

![Saccharin Structure](image_url)

**6-methyl-1, 2, 3-oxathiazine-4(3H)-one 2, 2-dioxide**

Acetsulfame potassium (23) also, known by the name Acetsulamide K or Ace K. It is non-nutritive sweetener with 200 times sweeter than sucrose but has a slight bitter after taste when added to foods or beverages at high concentration. Some researchers reported that Acetsulfame K may increase the occurrence of breast cancer in laboratory animals, but FDA maintains its safety status (23).

Acetsulfame K is stable under heat and under moderately acidic conditions. This stability properties making Acetsulfame K suitable for baked goods, carbonated beverages, protein shake, pharmaceuticals and in any other products that required a long shelf life. Its Acceptable Daily Intake (ADI) (19) (23) is 15 mg/kg body weight and it is marketed under trade name Suncett®.
Cyclamate: 

Cyclamate (24) is the sodium salt of cyclamic acid. It is 30 to 50 times sweeter than sucrose and it is marketed as a table top sweetener under trade name Twin® in Canada and over 50 countries.

In 1970 Cyclamate was banned from United States because laboratory experiments showed that large doses of cyclamate in a diet caused bladder cancer in rats. Recently United States lifted its ban (25) after the Cancer Assessment Committee of the FDA decided that cyclamate is not carcinogenic (26). Its acceptable daily intake (ADI) (25) is 11 mg/kg body weight.

Conclusion

High-intensity sweeteners (HIS) are non-nutritive ingredients used to sweeten and enhance the flavor of foods and are commonly used as sugar substitutes or sugar alternatives (26) and like all other ingredients added to foods, beverages and other products it must be safe for consumption.

High intensive sweeteners (HIS) from natural sources are refer to natural sweeteners and considered to be safe with GRAS status. The two natural sweeteners Rebaudioside-A extracted from Stevia leaves and Mogrosides extracted from Luo Han Guo (Monck fruit) were considered to be safe with GRAS status in the year 2008 and 2010 respectively.

Semi-synthetic peptides such as Aspartame and Neotame and synthetic chemicals such as Saccharine Sucralose, Acesulfame potassium, and Cyclamate, are not natural and refer to artificial sweeteners.

These artificial sweeteners before being approved must undergo extensive safety evaluation in tests with humans and animals and must meet the same standard of safety for consumption by consumers including pregnant women and children. In United States, these artificial sweeteners were approved by FDA as safe for applications as food additive sweeteners in foods, beverages and pharmaceuticals.

Because high-intensity sweeteners are many times sweeter than table sugar (sucrose), smaller amounts of high-intensity sweeteners are needed to achieve the same level of sweetness as sugar in foods.

Plus the availability of a variety of low-calorie sweeteners (27) for use in foods expands the capability to develop reduced-calorie products that better meet consumer needs and desires. In addition, blending some low-calorie sweeteners in foods and beverages may also act synergistically to produce the desired level of sweetness with smaller amounts of each sweetener and resulting taste often better meets consumer expectations of a sweetness profile close to that of sugar.

People may choose to use high-intensity sweeteners (HIS) in place to sugars for a number of reasons (28), including to these HIS do not contribute calories or only contribute a few calories to the diet.

High Intensive sweeteners assist people in losing weight, avoiding obesity diseases and other health associated with high caloric intake by replacing common sugars such as sucrose, dextrose, high fructose corn syrup and corn syrup in foods and beverages with these non-nutritive, zero calorie high intensive sweeteners without changing people’s diet habits and taste.

Assist diabetics to control their blood sugar levels without scarifying their regular diets and taste. Also, Patients with reactive hypoglycaemia (29) producing excess insulin (30) after the break down of complex carbohydrates or sucrose in their diets into glucose that is released into the blood stream and quickly metabolized causing blood glucose levels to fall below the proper level for the body and brain function.

As a result, these patients like diabetes, must avoid consuming foods containing high-glycaemic index ingredients (30) such as complex carbohydrates or sucrose and must choose foods containing sugars substitutes such as the high intensive sweeteners as alternative.

There are other several advantages for the application of high intensive sweetener in foods, beverages, candies, chewing gums and other products. For example, these High intensive sweeteners are non-fermentable by oral microflora. This non fermentable property helps consumers to prevent dental plaque and decay.

Other examples that benefits both consumer and manufacturers are the wide range stability of pH and temperature for these high intensive sweeteners that allows its applications in products required long shelf life at room temperature.

Consumers’ concern for weight management is the major market demand for these zero calorie high intensity sweeteners as a replacement for sugars in their diets and the worldwide consumption of these low calorie high-intensity sweeteners is largely
dependent on the production of diet carbonated soft drinks and low-calorie foods. Beverages market are the largest end-use for these high-intensity sweeteners, followed by foods, tabletop sweeteners, personal care products (such as toothpaste), and pharmaceuticals.

The World Health Organization estimates that there are over a billion people globally who are overweight and over 400 million of which are obese. Unfortunately, these numbers are expected to continue increasing and the market demand for these zero calorie, non-nutritive High intensive sweeteners (HIS) will increase. It is estimated that the global market of high intensive sweeteners for the year 2014 was 9.4 billion and it is expected to reach 9.9 billion by the year 2016. The old discovery Saccharine is the only high intensive sweeteners that is facing tough competition from the newly discovered competitors and its market demand continue declining.

Despite these zero calorie high intensity sweeteners are approved by FDA in United States and by similar organization in other countries and are recommended by physician or registered dietitian for a large segments of the population for several health reasons, some people continue to question the safety of these low calorie high intensity sweeteners in their diets.

In United States, FDA continues to maintain and review scientific literatures on the safety of these approved high intensive sweeteners in foods, beverages and other products.

In the case of new evidence suggested that a product containing the approved low calorie high intensity sweetener is unsafe, FDA is responsible to review such suggestion and take the proper action. Even, these extensive safety evaluations by FDA and by other similar organizations worldwide it did not change the safety concern of some people worldwide.

Conflict of interests: We declare that we have no conflict of interests.

References


3. Food Standards Australia New Zealand: "Food Standards Australia New Zealand: Aspartame what it is and why it's used in our food". Retrieved 09-12 (2008).


12. The potential intake of phenylalanine that may result from use of neotame as a general-purpose sweetener does not pose any safety concern." (FDA comments in Federal Register / Vol. 67, No. 131 / 2002 /pp. 45300-10).


Copyright © 2014 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. All Rights reserved by international journal of Natural Science and Discovery